

Remarks

Claim 3 was amended so as to clarify an ambiguity relating to the R₂ group.

Please note that, in the Preliminary Amendment filed by Applicant on July 3, 2003, Claim 3 (once amended) was restated and mistakenly represented as being the then current version of Claim 3. This was an error. Instead, Applicant should have restated Claim 3 (thrice amended), filed April 12, 2002, as the then current version of Claim 3. The Thrice Amended version of Claim 3 differs from the Once Amended version of Claim 3 by the elimination of "hydrogen, carbobenzyloxy-, and carbobenzyloxy-valine-" from the definition of R₁. Applicant's inaccurate restatement of Claim 3 in the Preliminary Amendment may have caused the Examiner to enlarge the scope of his prior art search unnecessarily. Applicant apologizes for this.

In any event, the statement of Claim 3, as amended herein, is accurate.

Claim 11 has been amended so as to reintroduce the "stereochemically pure" limitation.

Claim 18 has been amended so as to make it an independent claim.

Rejection under 35 U.S.C. § 103(a):

Claim 3 is rejected under 35 U.S.C. § 103(a) as obvious over Handa. Applicant traverses this basis for rejection. Example 85 of Handa is a compound approximately corresponding to the compound of Claim 3, except that R₁ includes only a single amino acid, viz., carbobenzyloxy-cysteine-. As amended, Claim 3 now requires that R₁ always has two amino acids. Applicant's amendment obviates this basis for rejection.

Rejection under 35 U.S.C. § 103(a):

Claim 3 is also rejected under 35 U.S.C. § 103(a) as obvious over Slee. Applicant traverses this basis for rejection. Compound 8 of Slee is a compound approximately corresponding to the compound of Claim 3, except that R₁ is carbobenzyloxy-. As amended, Claim 3 now requires that R₁ always has two amino acids. Applicant's amendment obviates this basis for rejection.

Rejection under 35 U.S.C. § 103(a):

Claim 11 is rejected under 35 U.S.C. § 103(a) as obvious over Jadhav. Applicant traverses this basis for rejection. Examples 91 and 93 of Jadhav are analogs of the compound of Claim 11. Example 91 of Jadhav employs a glycine residue where the compound of Claim 11 employs an alanine. Example 93 of Jadhav employs a leucine residue where the compound of Claim 11 employs an alanine. The disclosed synthetic route and isolation of both Examples 91 and 93 would indicate that these compounds are not stereochemically pure. The IC₅₀ for inhibition of an HIV protease fragment is reported by Jadhav to be 0.042 mg/ml (**47.7 μM**) for Example 91 and 0.099 mg/ml (**99.5 μM**) for Example 93.

In contrast, the compound of Claim 11, which corresponds to both compounds **1b** and **1200** is disclosed in Figure 10 of the present application to have an IC₅₀ for inhibition of HIV protease of **3.8 nM**, i.e., approximately 4 orders of magnitude greater than the reported activity for Examples 91 and 95 of Jadhav. This is surprising and unexpected. Furthermore, Claim 11 has been amended so as to be directed to a stereochemically pure compound. Applicant would note that there are 16 possible stereoisomers of the compound of Claim 11.

Figure 1 of the present application illustrates the binding of the compound of Claim 11 (compound **1b**). The importance of the alanine side chain of compound **1b** with respect to binding to HIV and FIV protease is discussed in the specification in the

bottom paragraph of page 6 of the specification.

Although, in many contexts, leucine may be considered a homolog of alanine, the present application teaches that the size of the alanine side chain is important for binding to HIV and FIV protease. The reported differences in activities supports this teaching. Indeed, the very low IC_{50} activities of the Jadhav compounds teaches away from the compound of Claim 11.

Accordingly, the compound of Claim 11 is patentably unobvious. Withdrawal of the obviousness rejection over Jadhav is respectfully requested.

Summary:

Applicant requests that the obviousness rejections be withdrawn and a Notice of Allowance be provided with respect to claims 3, 6-9, 11, and 16-22.

Respectfully submitted,



Donald G. Lewis
Reg. No. 28,636
The Scripps Research Institute
10550 N. Torrey Pines Road TPC-8
San Diego, CA 92037
February 2, 2004
(858) 784-2937